Current Management of Neonatal Abstinence Syndrome Secondary to Intrauterine Opioid Exposure

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Neonatal abstinence syndrome (NAS) comprises a constellation of drug-withdrawal symptoms that result from chronic intrauterine exposure to a variety of substances, including opioids, benzodiazepines, barbiturates, selective serotonin reuptake inhibitors, ethanol, nicotine, and caffeine. Most nonopioid fetal drug exposures result in limited clinical presentation, respond well to supportive care measures, and rarely require pharmacologic intervention.[1,2] Chronic in utero exposure to opioids is well characterized and is particularly problematic because of its high prevalence and frequent need for pharmacotherapy to mitigate withdrawal signs, especially when the opioid exposure is in the broader context of maternal polysubstance consumption.

Epidemiology of NAS

In a recent national survey, 18.3% of pregnant teens, 9% of pregnant women ages 18-25 years, and 5.9% of all pregnant women reported some illicit drug use.[3] Opioids specifically are ubiquitous and the upsurge in use is contemporaneous with pain management standards set by the Joint Commission on Accreditation of Healthcare Organizations in 2001. Correspondingly, there has been a 5-fold increase in opioid use during pregnancy during the last decade, with a prevalence of 5.6 per 1000 hospital births.[4-7]

The state of Ohio recently reported a 5-fold increase in the frequency of maternal drug abuse and dependency diagnoses at the time of delivery that were related to opioids, placing it second only to marijuana, and a 6-fold increase in hospitalizations due to NAS (from 1.4 to 8.8 per 1000 live births) in less than a decade.[8] The incidence of NAS has also tripled nationally, affecting 47%-57% of infants born to mothers on methadone or buprenorphine maintenance therapy.[7,9] The economic burden posed by these trends is staggering, with average hospital inpatient cost as high as $59 500 per hospital birth for infants with NAS.[8] In 2011, the treatment of NAS was associated with more than $70 million in charges in the state of Ohio alone. Medicaid was the primary payer source for 85% of NAS discharges during the same timeframe, which is significantly greater than the percentage of all Ohio births billed to Medicaid (55%).[8]

Clinical Presentation of NAS

NAS manifestations are modulated by a combination of maternal and neonatal factors, including the opioid dose, frequency and timing before delivery, maternal pharmacokinetics (PK), placental metabolism, concurrent medications, and neonatal PK and pharmacogenomics. The clinical presentation of NAS reflects a greater abundance of opioid receptors in the nervous system and the gastrointestinal tract. These may exhibit as neurologic excitability (eg, tremors, irritability, increased muscle tone, frequent yawning or sneezing, seizures), gastrointestinal dysfunction (eg, feeding difficulty, uncoordinated sucking, vomiting, diarrhea, poor weight gain), and autonomic signs (eg, diaphoresis, nasal stuffiness, fever, mottling, temperature instability). Other signs include respiratory distress and skin excoriation. The exact mechanism implicated in signs of NAS remains unclear, although it may result from increased adenylyl cyclase activity and norepinephrine release upon cessation of mu-opioid stimulation after birth.[10]

In the absence of evidence to substantiate alternate diagnoses, a careful maternal history of alcohol, tobacco, and prescription and nonprescription drug use should be ascertained with one of several tools, including the popular 4Ps Plus (ie, Parents, Partner, Past, Pregnancy).[11] Risk factors associated with maternal substance abuse include lack of prenatal care, premature delivery, sexually transmitted infections such as hepatitis C virus and HIV cigarette smoking, fetal intrauterine growth restriction, and poor maternal nutritional status.[12] In contrast, the risk of developing NAS is reduced by the lack of polysubstance exposure, prematurity, and minor alleles in the mu-opioid receptor (*OPRM1*) and catechol-O-methyltransferase genes.[13,14]

Clinical suspicion of intrauterine opioid exposure may be corroborated by the use of toxicology screening adapted for

AAP	American Academy of Pediatrics
NAS	Neonatal abstinence syndrome
OPRM1	Mu-opioid receptor
PD	Pharmacodynamics
PK	Pharmacokinetics

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urine, meconium, hair follicle, or umbilical cord tissue.[15] Umbilical cord analysis may be advantageous because of comparative ease in obtaining samples, relatively rapid availability of testing results (slower than urine but faster than meconium), and results that are comparable with meconium analysis.[16] In many cases, a positive opioid screen will trigger confirmatory testing that can distinguish the specific drug of exposure (eg, heroin from fentanyl). These additional results may be helpful clinically to determine the source of drug exposure and ultimate risk for withdrawal (eg, a screen positive for fentanyl is likely related to medication received during labor and holds no risk for withdrawal from short delivery exposures). Also, clinicians should know which opioids are screened by the test they are ordering, because it may not identify the presence of all drugs of abuse (eg, buprenorphine or methadone might not be included in the screen). Clinicians should order toxicology screens that will detect common opioid exposures in their patient population.

Hospital charges for urine, meconium, and umbilical cord tissue toxicology screening are relatively comparable, costing $300-$550, $250-$500, and $400-$800, respectively. It should be noted, however, that charges vary between institutions depending on the total number of drugs screened, where the analysis is performed (eg, in-house vs third-party service vendor) and additional charges incurred for confirmation testing. Recent developments in high-end tandem mass spectrometry techniques hold promise for both the identification and quantification of drugs and active metabolites. Local availability of such technology at competitive prices is possible and could expedite meconium toxicology screens, thereby contributing to utility in medical decision-making.

Assessment Tools for NAS

The Neonatal Intensive Care Unit Network Neurobehavioral Scale was developed for use in the neonatal intensive care unit to better understand the long-term implications of intrauterine exposure to opioids.[17] Although the complexity of this comprehensive and sensitive research tool makes its routine use for clinical purposes impractical, it shows that opioid-exposed infants demonstrate high levels of dysregulated behavior and stress, it is predictive of worse neurodevelopmental outcome, and it may be useful in identifying behavioral dysfunction that is amenable to early intervention.[17-19] Limited available data suggest that infants exposed to methadone are more likely to have a lower IQ, exhibit attention deficit/hyperactivity disorder, and receive other disruptive behavior diagnoses. However, these findings should be interpreted with caution because of confounding variables such as environmental, genetic, and socioeconomic factors. More studies will be needed to delineate the risk associated with exposure to non-methadone opioids.[20]

Infants at risk for NAS should be monitored diligently during the initial days after birth. Several standardized scoring systems have been developed to assist in identification, quantification of severity, and assessment of response to treatment of term infants with NAS. These include the Finnegan Neonatal Abstinence Severity Score, Lipsitz tool, Neonatal Narcotic Withdrawal Index, and Neonatal Withdrawal Inventory.[21-24] Although careful training of the staff using these assessment tools can increase interrater reliability, scoring mechanisms remain substantially subjective. In addition, the reduced capacity of preterm and ill infants with in utero opioid exposure to exhibit typical signs of withdrawal limits generalizability. For example, preterm infants may demonstrate less signs of withdrawal because of neurologic immaturity, whereas therapy administered to ill infants may impede full evaluation of withdrawal (eg, intubation, sedation, nil per os [nothing by mouth]).

Despite these shortcomings, the authors' practice aligns closely with recommendations from the American Academy of Pediatrics (AAP), which strongly encourage the use of protocols for the evaluation and management of newborn withdrawal and the use of standardized scoring systems with which the staff is comfortable.[25] Although standardization of treatment is known to enhance outcomes in many areas of medicine, to our knowledge there are no published NAS-specific data that demonstrate reduced length of stay or other clinically important outcome with the use of a protocol. However, the lack of such data should not preclude practitioners from exercising good clinical judgment and implementing sound evidence-based protocols.

Management of Infants at Risk for NAS

The risk of withdrawal is variable and is related to the type of opioid, dose, and timing of exposure. The AAP recommends that infants exposed to shorter half-life drugs and who manifest no signs of withdrawal could be safely discharged after 3 days of observation, whereas it is reasonable to monitor infants exposed to drugs with a longer half-life, such as methadone, for a longer period of time (4-7 days).[25] The authors' institutional policy calls for universal maternal drug screening during parturition, a minimum 72-hour observation for shorter half-life drugs implicated in withdrawal, and a minimum 96-hour observation for infants exposed to methadone or buprenorphine in utero.

The paucity of evidence to support any single treatment strategy has resulted in active debate as to the most effective management strategy. This is at least partially attributable to the absence of data on long-term outcome to compare infants who have exposure to opioids in utero without withdrawal with those who develop signs of withdrawal only requiring nonpharmacologic management and with those who ultimately develop symptoms severe enough to merit pharmacologic treatment. Every nursery, however, should adopt a standardized protocol for assessing and managing infants at risk for NAS, including a specified minimum duration of observation. The staff should be trained in administering the assessment tool selected by the nursery.

Nonpharmacologic Treatment of NAS

Mothers participating in opioid-treatment programs should be encouraged to breastfeed their infants; active or recent